# Medical Staff Conference

## Acute Renal Failure

*These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.*

DR. LAWRENCE Z. STERN:* The patient is a 53-year-old white man, a steelworker, who was admitted to the hospital for evaluation and treatment of acute renal failure. He had smoked two packs of cigarettes a day for over 30 years but was well until, nine months before admission, he noticed a slight tickling sensation in his throat. Eight months before admission his dentist noticed a mass growing in the posterior pharynx. Soon afterward, on diagnosis of carcinoma of the larynx, total laryngectomy and right radical neck dissection was performed. The patient did well and after several months returned to work. On the day before the present admission to hospital, he had a generalized convulsive seizure followed by several more seizures that evening. He had had no past history of a convulsive disorder, and there had been no exposure to toxic chemicals or drugs. The day following the seizures he was admitted, in status epilepticus, to a hospital in his community. At that time the body temperature was 41.5°C (106.8°F) the seizures were controlled with intravenous diphenylhydantoin (Dilantin®) and phenobarbital. There had been no fall noted in blood pressure throughout the course of illness. Urine output was 1,100 ml on the first day. It dropped, however, to 300 ml on the second day and was down to 100 ml per day by the fifth hospital day. Serum creatinine, which had been normal on admission, rose to 11.0 mg per 100 ml. On the seventh day, urine output rose slightly to 128 ml. In an attempt to effect diuresis, he was given 25 gm of mannitol intravenously, and at the same time a continuous intravenous infusion of mannitol was started. Over the next four days the patient received 1,500 ml of 20 per cent mannitol per day. During this period, urine output rose to a peak of 750 to 800 ml a day. However, on the tenth hospital day the output again dropped sharply. At that time the patient was noted to have acute parotitis, which was treated with intravenous penicillin and chloramphenicol. Elevated serum potassium levels were corrected by administration of potassium resin. Peritoneal dialysis was attempted but was mechanically unsuccessful. The patient was then transferred to this hospital.

On admission he was stuporous, was twitching constantly, and his breath had a uremic odor. The pulse was 100 and regular, respirations 28 to 30 per minute, blood pressure 156/90 mm of mercury and temperature 36.5°C (97.7°F).

On physical examination, signs of bilateral pleural effusion and pneumonia were noted, a pericardial friction rub was heard and the abdomen was tender but difficult to evaluate because there was fluid within the subcutaneous tissues.

Packed cell volume was 37 per cent and leukocytes numbered 18,600 per cu mm with a shift to the left. Serum sodium was 118 mEq, potassium 2.8 mEq, carbon dioxide 14.8 mEq, and chloride 72.5 mEq per liter. Serum creatinine was 13.6 mg per 100 ml, blood urea nitrogen 116 mg per 100 ml, and serum osmolarity 417 milliosmoles per kg of water.

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On the evening of admission hemodialysis was carried out for six hours, during which the serum osmolarity fell to 246 milliosmoles, creatinine to 7.8 mg and serum electrolytes returned to normal, the patient becoming quite alert. In the next few hours diuresis began and the total urinary volume reached six liters per day. From then on, there was rather dramatic and remarkable recovery from renal failure.

Recovery was complicated by pneumonia (*Pseudomonas aeruginosa* was cultured from sputum) which has been successfully treated with low doses of colistin. A density has appeared on an x-ray film of the chest which may represent a recurrence of laryngeal carcinoma or a second primary neoplasm.

DR. WARREN RUSSELL:** A film of the chest taken on the day of admission demonstrated a diffuse* increased density in both lung fields, but particularly on the right. Part of the density was due to an effusion. Following therapy, the lungs were shown to be clear except for a large lesion which appeared at the right base. As it was a solitary large mass, it was considered most likely a second primary neoplasm, but a metastatic or even a granulomatous lesion could not be excluded. An intravenous pyelogram demonstrated rather poor concentration bilaterally but no evidence of obstruction.

DR. PAUL F. GULYASSY:† The unusual derangements encountered in this patient make an excellent introduction to a discussion of the therapy of acute renal failure. We can come to generalities later, but first the case at hand:

This patient had moderate azotemia and hyponatremia, and clinical examination showed a decided increase in extracellular fluid volume as evidenced by extreme pitting edema. In addition, one could infer other extremely important disturbances. The serum osmolarity when first measured was 417 milliosmoles per kg of water. If one takes

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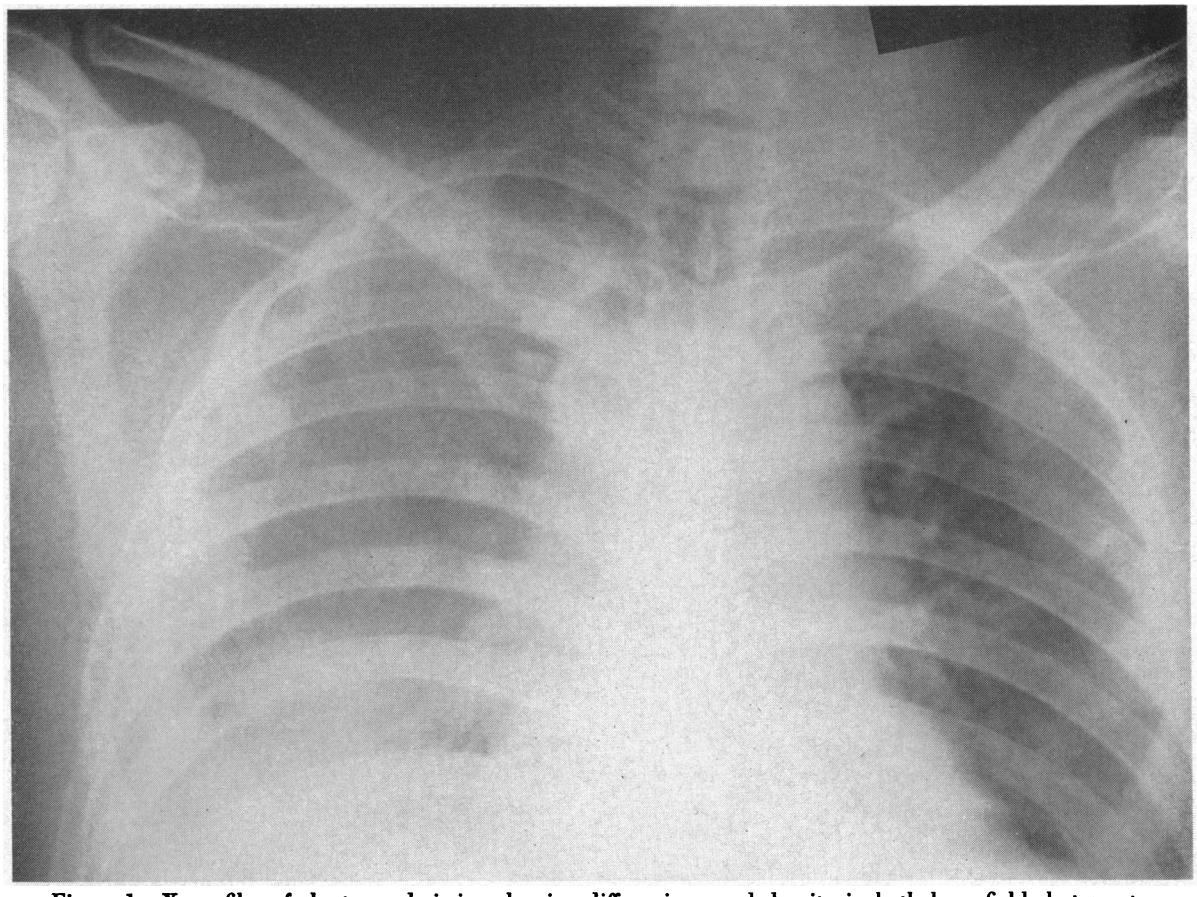

**Figure 1.—X-ray film of chest on admission showing diffuse increased density in both lung fields but greater on the right.**

the sum of the serum sodium concentration and the blood glucose and adds an additional factor of approximately 10 to 15, as was shown by the very extensive studies of Dr. Isidore Edelman and Dr. Frank Gotch, a very close approximation of the actual serum osmolarity may be obtained unless there is present some other osmotically active substance. In this patient the sum of all the osmotically active substances was approximately 300 milliosmoles, leaving an osmotic gap of 117 milliosmoles per kg of water, which we infer is the concentration of mannitol. This means that the concentration of mannitol was approximately 2,100 mg per 100 ml in the extracellular space. The administration and retention of so large a quantity of a substance which is retained in the extracellular fluid volume produces a series of consequences, some of which are obvious, some not. As one injects hypertonic solutions intravenously, there is movement of water out of the cells into the extracellular fluid space along the osmotic gradient, and dilution of the serum sodium concentration results. In this patient serum sodium was 118 mEq per liter when he entered the hospital. This change may also be due to urinary sodium losses. The movement of water out of cells causes cellular dehydration, which is very difficult to estimate. However, in this patient, the extent to which the blood mannitol was raised above and beyond the depression of serum sodium concentration suggests a 25 per cent loss in intracellular water at the time treatment was begun.

We were faced with three problems: an extraordinary degree of hyperosmolarity, pronounced expansion of the extracellular fluid volume, and decided contraction of the intracellular fluid volume. Therapeutically, two changes had to be made: one was to expand and dilute the intracellular volume to normal, and the other was to contract and dilute the extracellular volume. To handle these problems, dialysis was carried out. The indications which make one lean toward peritoneal or hemodialysis depend on multiple factors, but in this case the critical factor was the relative effects of the two techniques in terms of the manipulation of the patient's water volumes and total solute concentration. Peritoneal dialysis in this patient would have exposed him to a relatively dilute solution of a normal osmolarity. This would have produced osmotic movements of water into

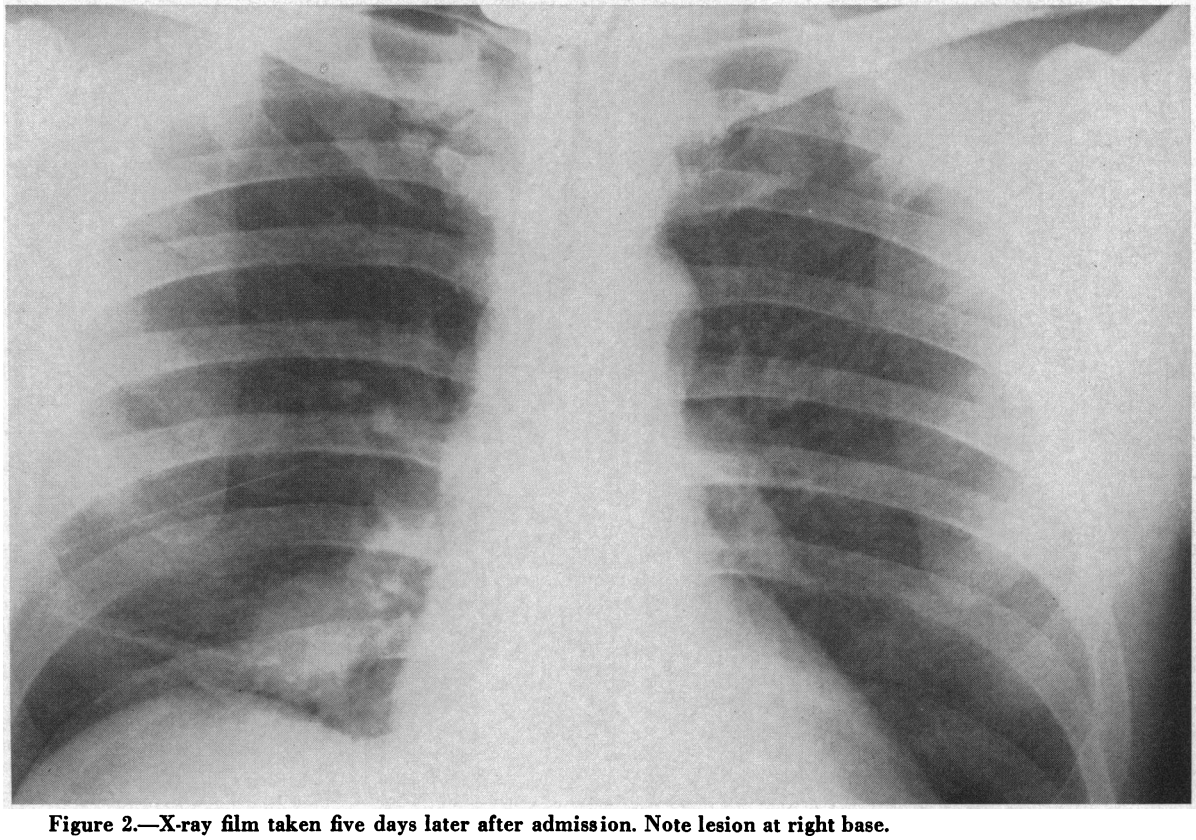

**Figure 2.—X-ray film taken five days later after admission. Note lesion at right base.**

the extracellular fluid volume, which would have been an undesirable effect, producing further expansion of the already increased volume of extracellular fluid. To dilute the patient's intracellular fluid and at the same time remove the excess extracellular fluid volume, hemodialysis at normal osmolarity but under increased pressure was undertaken. Dr. George Duffy will describe the patient's response to this form of therapy.

DR. MAURICE SOKOLOW:* Dr. Gulyassy, when you began your discussion of the present case, you indicated that you would turn later to a more general dissertation on the treatment of acute renal failure.

DR. GULYASSY: Because of the numerous pathophysiologic complexities the disease entails, it may be most profitable for purposes of general discussion to focus on certain aspects of therapy. One aspect of the problem of acute renal failure is the attempt made to arrest the process which often occurs before our eyes. This is probably the most frustrating aspect of the treatment of acute renal failure because, as in this patient, the precise pathogenesis of the renal injury is not at all clear. We attempt to restore blood volume where there is a possibility of hypovolemia and shock contributing to the onset of acute renal failure. Beyond this, little can be done to block the evolution of incipient renal injury. Therefore, it is not surprising that physicians over the years have attempted various measures which block the development of frequently lethal acute renal failure. In recent years the most widely publicized and misunderstood attempt at the prevention of acute renal failure has been the application of osmotic diuretic agents to sustain urine flow when the output is decreasing sharply, presumably due to a decrease in the circulation of blood to the kidneys. This is an extremely complicated subject and I will limit myself to a discussion of, first, those instances where osmotic diuresis is undoubtedly a very useful therapeutic maneuver; second, those instances in which the value is perhaps doubtful, but because of the urgency of the situation the therapy may be attempted; and third, and most important of all, the fact that this is not entirely a harmless procedure.

Turning to the first point, osmotic diuretic agents, particularly urea and sucrose, have been used since the 1930's. Currently mannitol has been most commonly used for this purpose. There are certain clear-cut situations where there is a very sound reason for using this approach. One such situation is the sudden appearance of pronounced uricosuria. Patients who are treated with chemotherapeutic agents, where there is rapid lysis of cells, often have a burst of uric acid excretion which reaches enormous proportions. In these patients, we are dealing with a simple problem of chemical solubility. Because of the very poor solubility of this compound, crystallization will occur if the volume of urine is reduced, followed by obstruction either outside the renal parenchyma or diffusely within the renal tubules. Therefore, the maintenance of high rates of urine flow will maintain the uric acid in a soluble form and abort mechanical precipitation of uric acid nephropathy.

A similar situation is massive hemolysis with the excretion of large quantities of hemoglobin. Here a similar physical consideration applies. We assume that by maintaining a brisk rate of urine output to keep the concentration of a coagulable protein at minimal levels, particularly in the distal nephron, precipitation and permanent obstruction throughout the kidney may be aborted.

A third situation in which osmotic diuresis may be indicated is prolonged cross-clamping of the aorta below the renal artery. The evidence as to the magnitude of the efficacy of mannitol here is not at all clear, nor is it clear whether other measures would not be as effective. Reported studies have shown that with the maintenance of urinary excretion before aortic cross-clamping, the incidence of oliguria after the clamping is done is certainly greatly diminished, and retrospective analysis indicates that the incidence of severe acute renal failure is also diminished.

Finally, there are certain situations in which the usefulness of the maintenance of diuresis for increasing urinary excretion and clearance of certain compounds is being evaluated. One such situation, which Dr. Frank Gotch has described in detail, is the use of mannitol diuresis to enhance the urinary excretion of barbiturates and thereby reverse the complications of barbiturate toxicity.

Now let us consider the problem of the patient with diminishing urine output, in whom one suspects incipient renal failure. In most varieties of acute renal injury there is surprisingly little evidence that inducing osmotic diuresis is effective in preventing the development of acute renal fail-

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ure. Therefore it is important to examine the other aspect of this problem, namely the hazards of using such an agent. Mannitol and other non-metabolizable polyalcohols are characterized by the fact that they distribute through the extracellular fluid space. They penetrate cells at an extremely low rate and are essentially non-reabsorbable from the filtrate in the normal kidney. If mannitol is injected into a normal person, the rising concentration as the filtrate moves down the tubule induces inhibition of sodium reabsorption, followed by diuresis which produces progressive clearance of the mannitol from the circulation. In the patient with a very limited renal excretion, the clearance of mannitol will depend upon the extremely limited extrarenal losses, which amount to approximately 5 ml per hour per kilogram of body weight. In a 70-kilogram patient this would be a net clearance of only 4 or 5 ml per minute, approximately 5 per cent of normal clearance by renal excretion. Therefore, repeated injection of this type of agent when there is no efficient route of excretion can produce progressive accumulation of the substance in plasma and extremely important disturbances in fluid and electrolyte patterns. Important histological changes, which may be related to the sudden appearance of renal failure as a secondary consequence to the administration of the osmotic agent have also been described. A striking pattern of vacuolization of the proximal tubule after injection of large quantities of glucose, sucrose or mannitol was termed "osmotic nephrosis" in the 1930's. This lesion in recent years has either been forgotten or assumed to be harmless. The present case and several similar ones, however, strongly suggest that this casual attitude is unwarranted.

DR. GEORGE DUFFY:*[1] As Dr. Gulyassy has said, the only method of removing this non-metabolizable material in the case of renal shutdown is either by dialysis or, possibly, by an exchange transfusion. Hemodialysis was begun and the patient's serum sodium, which was 129 mEq per liter 15 minutes after dialysis was started, was 146 mEq after six hours of dialysis. The blood urea nitrogen fell from 116 mg per 100 ml to 56 mg. The calculated serum osmolarity was 300 milliosmoles per liter at the beginning of dialysis and 313 at the end. The osmotic gap had decreased from 117 to 37 mOsmol per liter, which was a decrease from 2,100 mannitol of mg per 100 ml to 668 mg per 100 ml. At the end of dialysis the patient's mental status had greatly improved.

DR. SOKOLOW: Dr. Gotch, would you care to make any comment?

DR. FRANK A. GOTCH:*[2] As Dr. Gulyassy pointed out, mannitol may be of value in increasing urine flow in patients with transfusion reactions, acute hemolysis and acute hyperuricemia. Based on our experience in barbiturate ingestions, a loading dose of about 1 gm of mannitol per kilogram of body weight should initiate an osmotic diuresis of 300 to 500 ml per hour. Subsequent maintenance of mannitol to sustain the osmotic diuresis at this level will generally amount to about 0.5 gm of mannitol per kg of body weight per hour. It is important to note that the maximum concentration of mannitol achieved in the urine is about 350 milliosmoles per kg, or 5 per cent mannitol. Therefore, if 20 per cent mannitol is used, the urine volume must be at least four times the infused mannitol volume or there will be predictable accumulation of mannitol in the plasma. If 5 per cent mannitol is used, the urine volume should at least equal the mannitol volume.

## EDITOR'S FOLLOW-UP NOTE:

Following presentation at these rounds, the patient was transferred to the surgical service where right pneumonectomy was performed for a bronchogenic carcinoma of the right lower lobe. The postoperative course was uncomplicated and on the day of discharge from the hospital the serum creatinine was 1.4 mg per 100 ml.

Generic and Trade Name of Drug.
Dephenylhydrantoin—*Dilantin.*

### ACUTE RENAL FAILURE

Recent Summaries in the Literature

1. Merrill, J. P.: "Acute Renal Failure" in Diseases of the Kidney. Strauss, M. B., and Welt, L. G., Eds., Little, Brown and Co., 1963, pp. 445-468.

2. Boen, S. T.: Peritoneal dialysis in clinical medicine. Charles C Thomas, 1964.

3. Maher, J. F., and Schreiner, G. E.: Hazards and complications of dialysis. New Engl. J. Med. 273:370-377, 1965.

### MANNITOL NEPHROSIS

1. Maunsbach, A. B. et al.: Light and electron microscopic changes in proximal tubules of rats after administration of glucose, mannitol, sucrose or dextran. Lab. Invest. 11:421-432, 1962.

2. Lampe, W. T., II: Interstitial nephritis. Reversibility of osmotic nephrotic changes due to mannitol proved by renal biopsy. Angiology 16:281-287, 1965.

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*[2]Associate Clinical Professor of Medicine.